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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,117	07/12/2001	Tom W. Muir	3440-P02436US3	2865

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DANN, DORFMAN, HERRELL & SKILLMAN
1601 MARKET STREET
SUITE 2400
PHILADELPHIA, PA 19103-2307

EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,117	MUIR ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 12/11/03 is hereby acknowledged.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 1-12 are currently pending and under consideration.

Specification (Sequence Rule Conformance)

2. Applicant's specification amendment inserting proper sequence identifiers has been entered. Applicant's application now conforms with the Sequence Rules.

Withdrawn Objection (s) and/or Rejection(s)

Applicant's amendment and arguments have overcome the indefinite rejection of claims Claims 1-11 as recited in the prior office action.

Applicant's argument (e.g. referring to specification page 22, lines 5-7) providing specification support for the claim term "conjugated thiol" has overcome the claim objection for lack of antecedent support.

Applicant's arguments, the lack of motivation to combine cleavage/ligation in one step utilizing a conjugated thiol and the benefits imparted therefrom have overcome the following obviousness rejctions:

a. Claims 1, 4, 6, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comb et al. US Pat. No. 5,834,247 (11/98: filed 5/97 or earlier) and Dawson Science Vol. 266 (11/4/94) pages 776-779.

b. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comb et al. US Pat. No. 5,834,247 (11/98: filed 5/97 or earlier) and Dawson Science Vol. 266 (11/4/94) pages 776-779 as applied to claims 1, 4, 6, 8 and 9 above, and further in view of Kent WO 96/34878 and/or Dawson et al. JACS Vol. 119, No. 19 (5/97).

c. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comb et al. US Pat. No. 5,834,247 (11/98: filed 5/97 or earlier), Dawson(Science), Dawson (JACS) and Kent WO 96/34878 references as applied to claims 1-9 above, and further in view of Chong et al. Gene (6/97) pages 271-281.

Provisional obviousness double patenting of claims 1-11 over claims 1-11 of copending Application No. 09/879,744 is withdrawn in view of the abandonment of the '744 application.

Outstanding Objection(s) and/or Rejection (s)

Priority

3. With respect to claims 1, 4, 6, 8-10 and 12 which recite "conjugated thiol", Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32

USPQ2d 1077 (Fed. Cir. 1994). It is also noted that the limitation present in new claim 12 reciting the addition of an "alkyl ester" is not supported in the parent application nor any of the provisional applications and clearly represent NEW matter e.g. **the present application is a CIP of the parent 09/191,890.** See new matter in present specification at page 22, line 6 (insertion of "ethanethiol is a preferred reactant"); and bottom of page 28-top of page 29 referring to additional presence of alkylthiol "ramp up"). Accordingly, all the claims of the present application are afforded the filing date of the present application (e.g. 7/12/01) for purposes of prior art.

4. Claims 1, 4, 6, 8-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (lack of written description) and/or that the claimed invention is enabled for the full scope of using a "conjugated thiol".

The present claims are directed to a single pot method of cleaving a recombinantly expressed protein for generating a protein intermediate for ligation to a peptide containing an N-terminal cysteine which employs the use of "a conjugated thiol". In this respect, it is noted that the term "conjugated thiol" is not defined in a limited manner in the specification and thus includes "conjugated" alkyl as well as aryl compounds.

The specification description (e.g. see Markush of claim 2) is directed to aryl containing conjugated thiols which include specific thiophenol compounds containing

unsubstituted and specifically substituted thiophenols. For example, the specification on page 22 states:

> The thiophenol utilized in the present invention may be substituted or unsubsituted with thiophenol itself being preferred due to its commercial availability and reaction. Other equivalents are conjugated thiols such as 1-thio-2-nitrophenol, 2-thiobenzoic acid, 2-thiopyridine, **ethanethiol is a preferred reactant.** 4 thio-2pyridine carboxylic acid and 4-thio-2-nitropyridine. (Bolded emphasis indicates new matter not present in prior applications).

It is clear that the above-enumerated species of "conjugated thiols" on page 22 of the specification (e.g. 1-thio-2-nitrophenol, 2-thiobenzoic acid, 2-thiopyridine, 4 thio-2pyridine carboxylic acid and 4-thio-2-nitropyridine), while perhaps "representative" of conjugated ARYL thiols, are clearly not representative of conjugated ALKYL thiols. In this regard it is noted that ethanethiol is not representative of a conjugated alkyl thiol since it is not conjugated (e.g. possess alternating single/double bonds).

The specification (e.g on page 24) further discloses that out of the group of co-factors tested (i.e. DTT, N-acetyl cysteine, cysteine, mercaptoacetic acid, and thiophenol), "Surprisingly, thiophenol, was found to be the only co-factor tested that supports both efficient cleavage and efficient ligation": see specification page 24, especially lines 20-23). In this regard, if ALKYL thiols are unsuccessful (e.g. nonenabled) at achieving BOTH efficient cleavage and efficient ligation, whereas SUPRISINGLY thiophenol was found to be effecient at BOTH, applicant's own specification supports the criticality that ARYL (e.g. non-alkyl) conjugated thiol compounds are necessary to effect BOTH efficient cleavage and efficient ligation. This argument finds additional support in other parts of the specification which consistently

recite utilizing "a particular reagent, i.e. "thiophenol" to BOTH cleave and ligate. E.g. See specification page 7, lines 1-8.

Accordingly, the specification indicates the criticality of utilizing conjugated aryl (E.g. NON-alkyl) thiol compounds to effectuate both ligation and cleavage. There are no specification examples that indicate the utilization of a single conjugated alkyl compound **alone** that effectuates both ligation and cleavage. IN this regard it is noted that the specification's indication that the reaction may **further comprise** (E.g. see new claim 12:emphasis provided) an "alkyl thiol" does not remove the need for the presence of a conjugated aryl thiol compound to effectuate both ligation and cleavage.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Although directed to DNA compounds, this holding would be deemed to be applicable to any compound; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s).

In the present instance, the claimed invention contains no identifying characteristics regarding the scope of "conjugated thiol" compounds necessary to effectuate both ligation and cleavage. In this regard, it is noted that conjugated thiophenol core structure appears to be critical regarding the successful practice of the presently claimed invention as admitted (and discussed above) in the specification (e.g. "Surprisingly, thiophenol, was found to be the only co-factor tested that supports both efficient cleavage and efficient ligation": see specification page 24, especially lines 20-23). Additionally, the narrow scope of exemplified unsubstituted and substituted thiophenols are clearly not representative of the scope of the presently claimed "conjugated phenol" compounds.

Additionally, with regard to enablement, it is noted that compound claims (or method of use thereof) which **lack critical or essential subject matter** (e.g. critical core structure) which is nessary to the practice of the invention (e.g. binding a particular receptor) , but is not included in the claim(s) is not enabled (e.g. lacks utility) by the disclosure. See *Ex Parte Bhide* (Bd Pat. App. & Int.) 42 USPQ2d 1441.

In the present case, the claims directed to "conjugated thiols" for use to effect both ligation and cleavage lack critical chemical structure and thus are nonenabled for the full scope.

Discussion

Applicant's arguments directed to the above denial of 35 USC 120 priority and related 35 USC 112, first paragraph rejection were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above denial of

priority and 112 rejection was modified to conform to applicant's amendment (e.g. adding new claim); and additionally to include a scope of enablement rejection.

Applicant argues that the claimed term "conjugated thiol" is supported in the present specification since:

A. The term "conjugated" (defined as any compound having alternating single and double bonds) is art defined; and

B. The PRESENT specification (pages 22, lines 5-7) "provide a list of representative "conjugated thiols". This argument was considered but deemed nonpersuasive for the following reasons.

Initially, it is noted that the definition of a "conjugated" compound is not at issue; but the the above rejection addresses both the possession and enablement of the full scope of "conjugated thiols" which includes both aryl and alkyl containing thiols.

In this regard, the specification on page 22 referred to by applicant states as follows:

> The thiophenol utilized in the present invention may be substituted or unsubsituted with thiophenol itself being preferred due to its commercial availability and reaction. Other equivalents are conjugated thiols such as 1-thio-2-nitrophenol, 2-thiobenzoic acid, 2-thiopyridine, **ethanethiol is a preferred reactant.** 4 thio-2pyridine carboxylic acid and 4-thio-2-nitropyridine. (Bolded emphasis indicates new matter not present in prior applications).

It is clear that the above-enumerated species of "conjugated thiols" on page 22 of the specification (e.g. 1-thio-2-nitrophenol, 2-thiobenzoic acid, 2-thiopyridine, 4 thio-2pyridine carboxylic acid and 4-thio-2-nitropyridine), while perhaps "representative" of conjugated ARYL thiols, are clearly not representative of conjugated ALKYL thiols. In

this regard it is noted that ethanethiol is not reprsentative of a conjugated alkyl thiol since it is not conjugated (e.g. possess alternating single/double bonds).

Applicants "take exception to the Examiner's contention that the thiophenol structure is critical to the successful practice of the instant invention" as indicated by the above rejection's reference to the specification recitation that e.g. "Surprisingly, thiophenol, was found to be the only co-factor tested that supports both efficient cleavage and efficient ligation": see specification page 24, especially lines 20-23). Applicant goes on to argue that "It is clear when properly considered in context that this statement refers only to the group of tested co-factors mentioned in the previous paragraph, i.e. DTT, N-acetyl cysteine, cysteine, mercaptoacetic acid, and thiophenol. Of the listed co-factors, only thiophenol can be considered a "conjugated thiol".

However, if ALKYL thiols are unsuccessful (e.g. nonenabled) at achieving BOTH efficient cleavage and efficient ligation, whereas SUPRISINGLY thiophenol was found to be efficient at BOTH, applicant's own specification seems to support the criticality that ARYL (e.g. non-alkyl) conjugated compounds are necessary to effect BOTH efficient cleavage and efficient ligation. This argument finds additional support in other parts of the specification which consistently recite utilizing "a particular reagent, i.e. "thiophenol" to BOTH cleave and ligate. E.g. See specification page 7, lines 1-8. Accordingly, the specification indicates the criticality of utilizing conjugated aryl (E.g. NON-alkyl) thiol compounds to effectuate both ligation and cleavage. There are no specification examples that indicate the utilization of a single conjugated alkyl compound **alone** that effectuates both ligation and cleavage. IN this regard it is noted that the specification's

indication that the reaction may **further comprise** (E.g. see new claim 12:emphasis provided) an "alkyl thiol" does not remove the need for the presence of a conjugated aryl thiol compound to effectuate both ligation and cleavage.

Accordingly, denial of 35 USC 120 priority and the 35 USC 112, first paragraph rejection recited above is retained since the specification fails to provide sufficient support and/or enablement to satisfy 35 USC 112, first paragraph for the full scope of the term "conjugated thiols" for the reasons recited above.

5. Claims 1-12 are rejected under 35 U.S.C. 102(a,b) as being anticipated by Severinov et al. J. Biol. Chem. Vol. 273, (June 1998) pages 16205-16209.

Severinov et al. teach "expressed protein ligation" which comprises expressing a protein in a procarye (E.Coli) utilizing a vector (pCYB) in which the protein is bound to an intein-chitin binding domain (CBD) and the subsequent ligation (in situ, e.g. in a single pot) to a peptide containing an N-terminal cysteine having an unoxidized sulfhydryl side chain in the presence of a "conjugated thiol" (e.g. thiophenol), an "alkyl thiol" (e.g. dithiothreitol) buffer at pH @7 to effect cleavage of the protein-CBD to form a C-terminal protein thioester which forms a covalent bond to the peptide following an intramolecular rearrangement See abstract and entire article.

Discussion

Applicant's arguments directed to the above anticipation rejection were considered but deemed nonpersuasive for the following reasons. Initially, it is noted

that the above rejection was modified to address claims inadvertently excluded and the newly added claim.

Applicant argues that entitlement to 35USC 120 and 119(e) priority will serve to obviate the above rejection. This argument is not persuasive since 35USC 120 and 119(e) priority was denied for the reasons recited above.

Accordingly, the above rejection is hereby maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
March 29, 2004